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COLLAGEN DISEASE

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MARCH 1957

VOLUME XXXIV NUMBER 5

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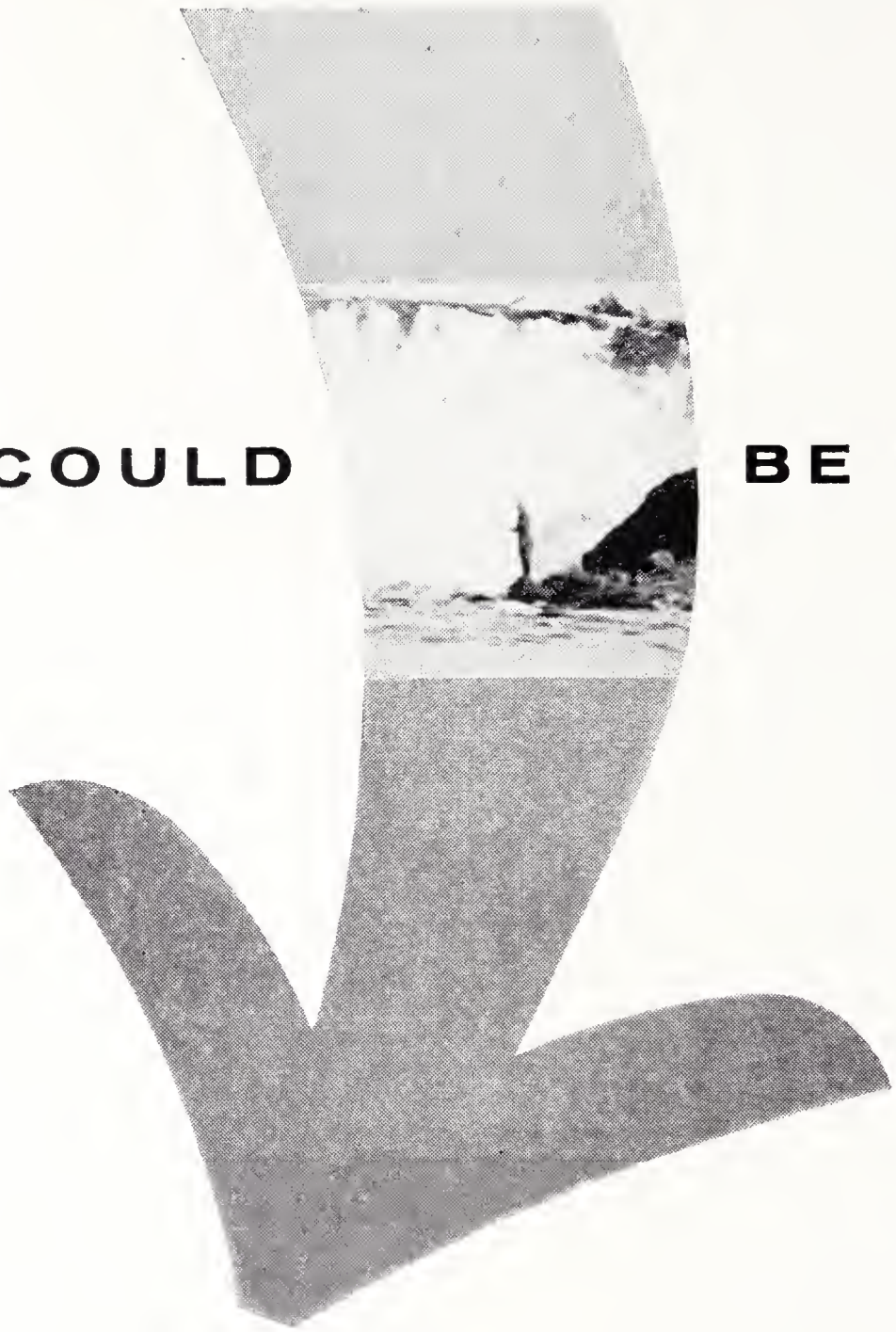

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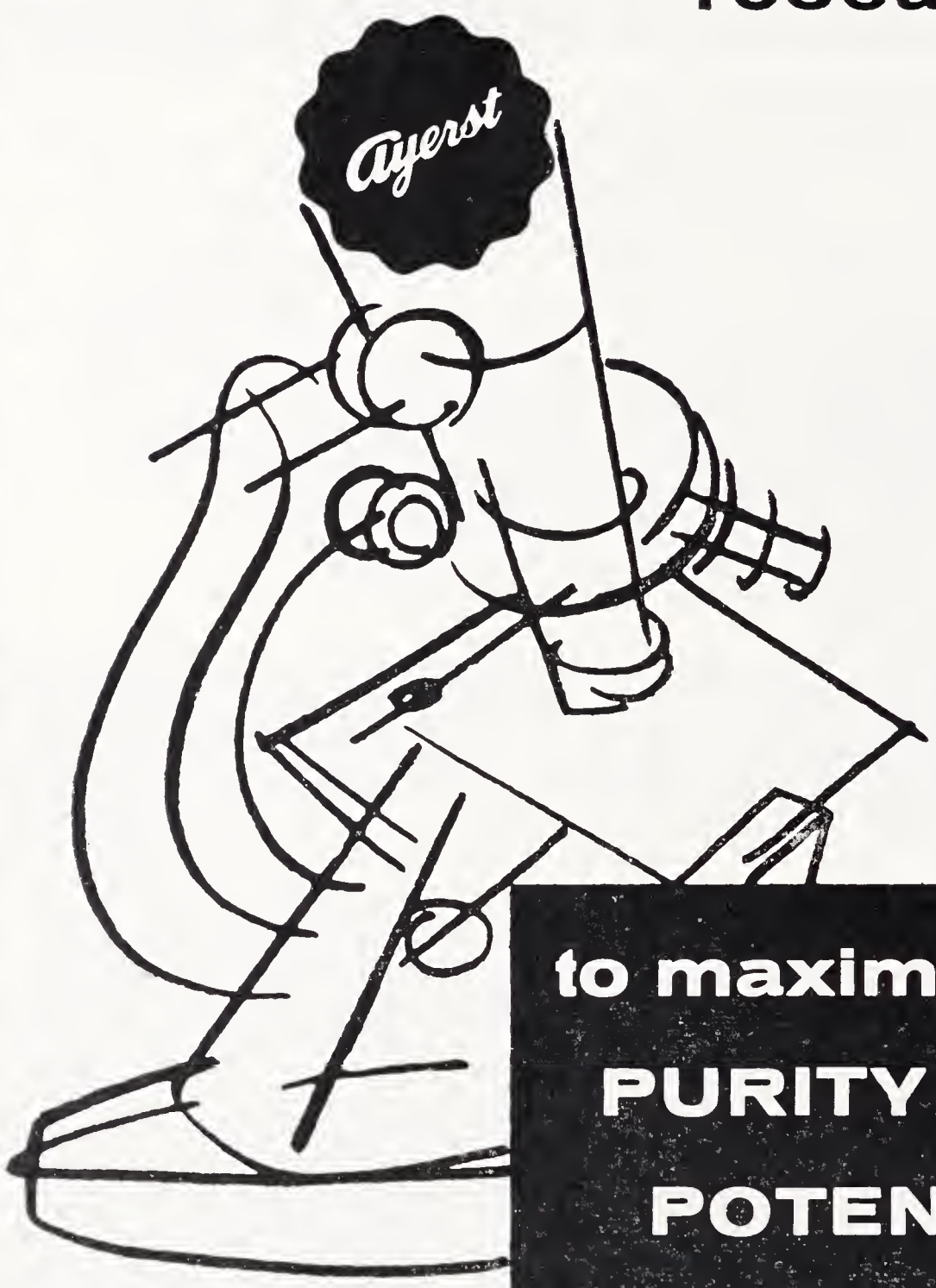

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EDITORIALS

Culture and Apathy

Recently we have heard an old familiar charge raised against the Journal; that it does not publish articles of wide enough interest for the junior years. The reason that we do not publish them is because we do not get them.

One of the primary aims of the Journal is the providing of a medium in which the student can get his writings published, and in virtually all cases, it is the only medium which is open to him. Since it is expected that most of the writing which a doctor will do subsequent to graduation will be medical, or at least scientific, it is not surprising that most contributors choose to write on medical subjects. With this we can find no basic disagreement. Due to the nature of the Journal we can select our non-scientific writing from only certain limited fields, which include; medical history or biographies, histories of the Medical School or some one of its functions, sketches of school life or people and essays on the profession, whether humorous or not. We must confess this does not make a very stimulating list. But one must remember that the Journal is not competing with collegiate year books or the periodicals published by the Arts colleges. It is in competition with other professional journals, and this rather drastically limits the type of material we can use. As for reports of various classes and general student news, there is a separate organ published by the Society for that purpose which can do this sort of thing better than we can. We must confess that we find the familiar complaint becoming a little tiresome, because the people who propose it have usually given little if any thought to the reasons why it should be so.

We cannot shift the blame however. It is the junior years who should be providing the non-medical writings for the Journal and for the past few years at least, the staff has failed to stimulate enough interest to produce good articles from the premedical and first, and sometimes even second medical years. And because these articles are not written, about half of the faculty of medicine finds nothing in the Journal to interest it. However, whether the Journal staff accepts a share of the responsibility for this failing or not, the junior years must accept their share as well. Appeals were made earlier in the year through the class presidents for people interested in working on the Journal; the results were singularly uninspiring. We do not expect overwhelming masses of applications for positions, this would be too much to expect, but it does hurt a bit for the editorial staff to be criticised later in the year for the results of this apathy. Must the medical student be cajoled, prodded and coaxed into everything? We hope not.

J.C.D.

On This Issue

In this issue of the Journal we present a group of papers diseussing the various types of eollagen disease. Our deeision to use this topie has already been questioned. We have been told by readers that the diseases are uneommon, rarely seen by students and never seen in general practiee. It is diffieult to reply to this eritieism but let us all remember the time we have spent learning about pernieious anaemia and the baeteriology of several tropieal diseases. These eonditions are also rarely seen by the student or the general praetitioner. One eannot deny their importanee. With newer methods of diagnosis and a general inereased awareness of eollagen diseases it seems eertain that cases will be more frequently reported. Beeause we feel that many eases are going undiagnosed, we believe this issue to be important and of some value to the reader.

Dr. M. A. Ogryzlo, an authority on the subjeet, has been most helpful in the preparation and editing of these papers. The Editors and authors would like to express their thanks for the time and assistance he has given.

It seemed most appropriate to publish this issue on the eve of the Ninth International Congress of Rheumatie Diseases. The meeting will be held in Toronto June 23-28 1957.

J.A.L.

WHAT IS COLLAGEN DISEASE ?

R. J. FOOTE, 5T7

THE various diseases classified as "collagen diseases" were recognized as distinct entities long before the term "collagen diseases" was introduced. For example the dermal manifestations of Lupus Erythematosus were first described in the literature by Biett in 1828, under the term "erythema centrifuge". Further contributions were made by Hebra in 1845 and by Cazenave in 1851. Kaposi described the disseminated form in 1872 and Osler noted the visceral manifestations of the disease in 1895.

The foundation for considering these diseases as systemic was actually laid by Morgagni in his description of organ pathology. To this basic concept was added Virchow's work on cellular pathology. Later combining the 2 theories, Bichat specified a "système cellulaire" and suggested that each tissue system reacts to stimuli in a uniform manner, regardless of its location in the body. He thereby suggested that there are systemic as well as local connective tissue diseases. These theories lay fallow until 1933 when Klinge recognized the significance of the intermediate substance of the connective tissue in the definition of the pathologic lesions of rheumatoid arthritis and rheumatic fever, viz. the presence of fibrinoid degeneration. He noted that the lesions produced in these diseases were similar to those occurring in rabbits made hypersensitive to foreign proteins. These consisted of intracellular changes, fibrinoid degeneration of collagen and myxomatous swelling of the ground substance. He therefore proposed that these lesions were manifestations of systemic connective tissue diseases, and also, that these diseases were the result of a hypersensitivity reaction to foreign proteins.

In 1941 Klemperer, Baehr and Pollack carefully reviewed 35 cases of Disseminated Lupus Erythematosus. They did not deny the role of hypersensitivity and came to the conclusion that the apparently unrelated lesions seen in this disease were in reality the same. These authors revived the "système cellulaire" concept of Bichat and felt that the lesions all had a common etiology. They published a further paper in 1942 in which they regarded the connective tissue as an organ which was the common seat of these abnormalities. The basic abnormality was felt to be in the colloidal, extracellular component of the connective tissue. In agreement with the paper of Banks in 1941 they noted a similarity in Disseminated Lupus Erythematosus, Scleroderma, Polyarteritis and Dermatomyositis. However they felt that there was no interrelationship among the diseases apart from a pathological similarity and that there was no basis for a hypersensitive etiology for the group as a whole. They coined the term collagen diseases to cover these similarities. Oberling in 1943 proposed that the change was due to abnormal protein metabolism rather than a degenerative change in collagen tissue. The introduction of the term Collagen disease was not intended to be used in a diagnostic sense, since it referred to one morphologic characteristic only and therefore could not define all the underlying morbid processes of the diseases grouped under this heading. Nevertheless the term Collagen disease has retained its popularity.

In 1947 Baehr and Pollack published a paper in which they reviewed the lesions of Disseminated Lupus Erythematosus and Scleroderma and compared

the morphological changes which may be seen in the two diseases that form the common denominator of the group. They stressed the fact, noted by Klemperer in 1941, that pathological similarity does not mean etiological identity. In this review they drew 5 conclusions:

(1) Connective tissue has functions of support and metabolism. Any injury to connective tissue results in one of three reactions:
   (a) fibrinoid degeneration;
   (b) necrosis or sclerosis;
   (c) cellular proliferation.
   These reactions may occur singly or in any combination.
(2) Fibrinoid degeneration may be due to either local or general causes.
(3) Fibrinoid degeneration is not specific enough to be used as a criterion for classification.
(4) Disseminated Lupus Erythematosus and Scleroderma are so dissimilar clinically that they are related neither to each other nor to any of the other so-called hypersensitivity reactions.
(5) An allergic etiology seemed improbable.

In 1948 Lyman-Duff reviewed the literature up until that time. In his view any and all functions performed by connective tissue were purely passive. The exchange reactions as well as the supporting mechanism were not due to any active connective tissue function. Connective tissue, being an integral part of all other organs, does not really constitute an organ system. He suggested that the so-called collagen diseases should not be regarded as systemic but as tissue diseases, while the universality of connective tissue would account for the many clinical pictures seen in these diseases.

However, the fundamental problems regarding the constitution and physiology of the intermediate substances of connective tissue are still shrouded in mystery. The carbohydrate components of the homogeneous ground substance have been throughly investigated, but the protein fraction is hardly known. The mode of fibre formation and its relation to the ground substance is still obscure. It is not surprising therefore, that the problem of the abnormal fibrillar masses, commonly called fibrinoid, has hardly been approached. Yet it is the dominant structural alteration in these diseases. Recent studies have suggested that fibrinoid is not altered collagen but rather a precipitate in the ground substance, resulting from abnormal physico-chemical changes. Neither can ground substance be regarded as an inert supportive structure, for it plays an important role in tissue nutrition, water and salt metabolism and in regulation of acid-base equilibrium.

Up to this point in the history of the collagen diseases the classification was largely on the basis of pathological similarities. In the last decade, increasing emphasis has been placed on the clinical similarities of this group of diseases, and the frequent overlapping of many of the manifestations in borderline cases, such that a clear-cut distinction often cannot be made. In a restricted sense the term Collagen disease has come to include systemic lupus erythematosus, scleroderma, dermatomyositis, polyarteritis, rheumatoid arthritis and rheumatic fever. In none of these diseases has a specific or effective treatment been devised although new hope was raised with the demonstration by Hench in 1948, that ACTH and cortisone would induce a reversal of symptoms in rheumatoid arthritis. Soon thereafter, cortisone and ACTH were used as therapeutic agents in disseminated lupus, with good results. Since then, all the diseases thus far classified as collagen diseases were tried on

these agents, with some beneficial effect, although complete suppression of the pathological changes could not be achieved.

In spite of the warnings of Klemperer that the term "Collagen Disease" was meaningless, it has become firmly established as a clinical term. To the original group various authors have added other diseases, including thrombangiitis obliterans (Stewart 1949); Schoenlein-Henoch's puerpura, erythema nodosum and glomerulo-nephritis (Becker 1949); serum reactions, drug sensitivities and blood group incompatibility (Sante and Wyatt 1951); temporal arteritis, malignant hypertension and endocardial fibroelastosis (Hill & Reilly 1951; Becker et al. 1953). This broad inclusion of many seemingly unrelated diseases under the heading of "collagen diseases", detracts to some extent from the value of the term. Because of the possible common etiology of these diseases it has been suggested by Aegester and Long that all mesenchymal tissues respond as a unit. They explain the changes on the basis of a disturbance of defence mechanisms. Selye on the other hand has suggested that they are manifestations of adaptation to stress and classifies them under diseases of adaptation.

The present state of our knowledge is outlined in Talbott's monograph "Collagen Diseases". He classifies under this term, Rheumatoid Arthritis, Rheumatic fever, Systemic Lupus Erythematosus, Polyarteritis, Systemic Scleroderma, Dermatomyositis and has also included a more recently described disorder. Thrombotic Thrombocytopenic Purpura. The inclusion of these diseases is based on clinical similarity (in some cases) and response to steroid therapy, as well as a pathological similarity of many of the lesions. The etiology is unknown in all these conditions, except for a toxic reaction to Hydralazine therapy which resembles Systemic Lupus Erythematosus with L.E. cell formation, or sometimes rheumatoid arthritis. In Dr. Talbott's monograph the lesions of Systemic Lupus Erythematosus are considered to be due to the deposition of depolymerized nucleic acids in the ground substance. The presence of a specific L.E. factor is believed to be responsible for the depolymerization, accompanied by an associated increase in gamma globulins. Polyarteritis is considered primarily a blood vessel change with degeneration of the media followed by inflammation and scarring; dermatomyositis, a muscle degeneration followed by non-suppurative inflammation and scleroderma, a decrease in elastic fibres and hyalinization of the deeper collagen structures. In thrombotic thrombocytopenic purpura there is a segmental accumulation of hyaline below the endothelum of blood vessels.

It is clear that our knowledge of these diseases is still far from complete. Many questions remain to be explained with regard to the etiology and pathogenesis and also the pathological changes of these strange "Collagen Diseases".

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SCLERODERMA—(Progressive Muscular Sclerosis)

R. F. MARTIN, 5T7

Definition

SCLERODERMA is a systemic disorder charaeterized by an alteration in collagenous tissue which ultimately results in a focal or diffuse sclerosis of the skin. Similar fibrotie changes may also occur in the deeper underlying structures and in certain visceral organs. Associated vasomotor disturbances of the Raynaud type frequently accompany the disease.

Scleroderma may oceur in two different forms: the cireumseribed benign form known as morphea, and the diffuse or systemie form which is usually considered along with the eollagen diseases. The present discussion concerns itself with the systemie variety.

Historical

The disease was described as early as 1634 by Zaeutus Lusitanus but was first called scleroderma by Gintrac in 1847. Calcinosis was recognized as part of the disease process in 1910 by Thibergier and Weissenbaeh. The generalized or systemic nature of the disease was emphasized by Osler in 1898, and by many other authors since that time. On this basis there has been a tendeney in recent years to refer to the disease as Progressive Systemie Sclerosis. The nature of the pathologieal changes amply justifies its inclusion among the collagen diseases.

Incidence

The disease is not rare. By comparison with other collagen diseases it is approximately half as common as Systemie Lupus Erythematosus and possibly twice as common as Dermatomyositis or Polyarteritis Nodosa. The peak incidence occurs in the third and fourth decades. While occasional instances of the disease have been reported in children, it is rarely encountered before the age of 15 years. The sex incidence shows a slight predilection for females. All races may be affected but a familial tendency has not been reeorded.

Etiology

The etiology of the disease is unknown. Many theories have been proposed, but none has been substantiated. Among those suggested have been:

(a) Hypersensitivity. This is suggested in view of its relationship to other eollagen diseases, but direct evidence for this is laeking.

(b) Acute Bacterial Infection. Scleroderma has been precipitated by a variety of infections, either systemie, or loealized to the hands and fingers.

(e) Disease of the Central Nervous System or the Sympathetie Nervous System. This has been proposed because of the associated vasomotor symptoms

and frequent trophic lesions of the extremities.

(d) Emotional factors have been blamed for the precipitation of symptoms in some cases.

(e) Primary capillary changes involving dermal structures.

(f) Endocrine Disorders. Various endocrine glands have been incriminated at one time or another including the thyroid, adrenals, gonads and the parathyroid glands, but none has been substantiated. Attempts to demonstrate abnormality of calcium metabolism to explain the tissue calcinosis have met with failure. Removal of the parathyroid glands in many patients has not altered the course of the disease. Moreover it has been shown that fibrotic changes precede calcification.

(g) Trauma and exposure to cold and dampness have been described as precipitating factors in some cases, but cannot be regarded as causative.

Pathology

Skin: Two types of lesion may be found.

1. The epidermis may be thin and atrophic with flattening of the rete pegs, associated with the deposition of dense, avascular and acellular collagen tissue in the underlying dermis. The elastic fibres are decreased and fragmented. Calcium deposits may be present in the deeper layers. Skin appendages are often decreased in number leaving only a few atrophic sweat glands.

2. The skin of the fingers may show increased keratinization and flattening of the rete pegs. Degenerative changes may be evident in the collagen tissue of the dermis with increased cellularity, while the blood vessels show fibrinoid degeneration, intimal proliferation or reduplication of the inner elastic membrane. Perivascular, small round cell infiltration may be evident.

Skeletal Muscle: Involvement of the skeletal muscles may be indicated by a low grade myositis, with perivascular lymphocytic infiltration, atrophy of the muscle fibres or a diffuse increase in fibrous tissue between the muscle bundles.

Gastrointestinal Tract: The oesophagus often becomes shortened and more patulous with decreased peristaltic activity. The mucous membrane is smooth, and the normal rugae flattened. Occasionally ulcerations are present. The remainder of the gastrointestinal tract may show atrophy of the mucosa, submucosa, and muscularis with fibrous replacement from the oesophagus to the sigmoid. Occasionally ulceration may be observed in the small and large intestine, but this is rare.

Lung: A diffuse or patchy interstitial fibrosis of the lung parenchyma is a frequent accompaniment of Scleroderma. The small arterioles may be involved by a thickening of their wall with narrowing of the lumen and may give rise to pulmonary hypertension.

Pleura: Fibrinous pleurisy, pleural effusion or a diffuse fibrosis of the pleura are not unusual.

Heart: Occasionally there may be pericardial effusion with a fibrinous pericarditis. A diffuse deposition of fibrous tissue may be present throughout the myocardium, unrelated to changes in the vascular supply.

Kidney: In the gross the kidneys may appear normal or may resemble shrunken arteriosclerotic kidneys. Microscopically there may be interstitial fibrosis with patchy atrophy of the tubules. The medium and small arteries and arterioles are frequently affected. The changes include fibrinoid degeneration or an unusual proliferation of loose, acellular connective tissue beneath the endothelium, with narrowing of the lumen and sometimes occlusion by

thrombi. This may result in areas of infarction. Hyalinization of the glomeruli or of Bowman's capsule are commonly observed and sometimes there may be a hyaline thickening of the basement membrane giving the appearance of the "wire-loop" changes seen in Systemic Lupus Erythematosus.

Clinical

The onset is insidious in most cases with malaise, arthralgia, and vasomotor changes affecting the hands and sometimes the feet. There is intolerance to cold with cyanosis of the digits and occasionally blanching similar to Raynaud's phenomenon. These may occur months or years before changes occur in the skin. The skin changes may appear in three stages:

1. Diffuse non-pitting edema, with obliteration of the normal folds.

2. The edema is gradually replaced by a fibrosis. The skin becomes hard with fewer wrinkles, develops a waxy sheen and cannot be raised from the subcutaneous tissues. A brown pigmentation may occur, either diffuse or mottled, along with areas of depigmentation.

3. Eventually the skin becomes atrophic and adherent to the underlying structures, interfering with joint movements. The mucous membranes become atrophic and indurated causing shrinkage of the gums, soft palate, and uvula. Telangiectasia and hair loss occur late. The hands are usually the first to be involved with gradual spread up the forearm and arm. Similar changes may occur in the feet. When the face is involved the lips appear thin and drawn, the nose is pinched and the forehead devoid of wrinkles. Small telangiectatic tufts may be present on the cheeks. Frequently there is limitation of jaw movement.

In the extremities the patient usually complains of stiffness, pain, decreased strength and easy fatiguability. Muscular weakness and atrophy are evident. The fingers become immobilized in flexion and normal use of the hands is restricted. There may be palpable calcium deposits in the subcutaneous tissues of the fingers. Trophic ulcers are common, and sometimes gangrene of the digits. When present the calcinosis is most common at pressure points and adjacent to joints, and may be associated with ulceration of the overlying skin.

Gastrointestinal symptoms may include dysphagia, epigastric distress, and anorexia. There is no correlation between the onset and the severity of the gastrointestinal and the cutaneous lesions. Dysphagia is probably the most common gastrointestinal symptom and is present in a large proportion of patients. The oesophagus is no longer contractile and permits a reflux of stomach contents causing oesophagitis or ulceration. Rarely the large bowel is dilated and atonic so that evacuation may be difficult.

Weight loss may be marked with generalized muscle wasting.

The commonest pulmonary symptom is a chronic non-productive cough with dyspnoea and orthopnoea. This may be the result of a decreased vital capacity associated with pulmonary fibrosis and pulmonary hypertension.

Cardiac symptoms are usually late and include dyspnoea, orthopnoea, palpitation and tachycardia. These may result from a pericarditis with effusion or myocardial fibrosis with cardiac insufficiency. Gallop rhythm, pulsus alternans, a pericardial friction rub and arrhythmias may be noted.

Impairment of renal function with hypertension occurs not infrequently in the terminal stages. The B.U.N. rises and there may be retinal haemorrhages and exudates.

Rarely in the nervous system, there may be peripheral neuropathy with paraesthesias.

Laboratory Findings

Urine analysis may show red blood cells, casts, and albuminuria when there is renal involvement.

The red cell count, white cell count, and differential are usually normal, although the Sedimentation Rate may be elevated in the acute phase.

The Wassermann is negative.

The B.U.N. is elevated only in the presence of severe renal damage.

A decrease in the serum abumin with some increase of the globulin fraction may be observed.

The serum calcium, phosphorus and phosphatase are normal.

Urine creatinine is increased where muscle degeneration is extensive.

Skin temperature is decreased due to a decreased capillary bed in the skin. Skin elasticity is decreased.

X-ray Findings

Soft Tissue: Calcification (calcinosis) may be demonstrated in a proportion of the cases usually appearing in the distal parts in the early stages and later more proximally.

Bone: Atrophy and absorption of the terminal phalanges may occur with decreased density and stippling of the bones.

Gastrointestinal: The oesophagus often appears normal but may reveal delayed transit in the lower portion due to decreased peristalsis or narrowing of its lower end. Occasionally ulceration may be present. Radiological changes in the small and large bowel are difficult to demonstrate but may show segmental dilatation and delayed emptying.

Chest: A diffuse interstitial fibrosis may be present with pleural or pericardial effusions or cardiac enlargement with hypertrophy. On fluoroscopy cardiac excursion may be decreased.

E.C.G. Findings

The E.C.G. may reveal various arrhythmias, low voltage inversion of the T-waves, left axis deviation and heart block of varying degrees.

Diagnosis

The diagnosis of Scleroderma is made primarily on the basis of the cutaneous and subcutaneous changes. In the early stages it may be confused with rheumatoid arthritis or Raynaud's disease.

Course

The course of the disease is unpredictable, varying from a few weeks to years. It has been known to last two to three decades. Early fatal termination is usually due to renal or cardiac failure. Death is most commonly due to intercurrent infections, cardiac or pulmonary failure, in patients already seriously debilitated. At any point the disease may go into a remission spontaneously and cease to progress. It has been estimated that 50% of the patients succumb within 5 years, the prognosis being poorer in those with visceral manifestations.

Treatment

The value of individual therapy is often difficult to estimate because of a tendency toward partial remissions.

General Management

1. High calorie and high protein diet.
2. Adequate rest.
3. Avoidance of infections and trauma to extremities.
4. Protection from exposure to cold and dampness.
5. Physical therapy for involved muscles and joints.

6. Maintenanee of an optimistic outlook.

Specific Medication

No specific medication has yet been shown to alter significantly the course of this disease.

ACTH, cortisone, hydrocortisone, prednisone, and prednisolone have proved to be of limited benefit in early eases, but have been disappointing in the later stages and in acute fulminating eases. The use of hormones often results in a sense of well-being and may be aeeompanied by a reduetion in pain and stiffness, with a decrease in the degree of subcutaneous edema and inereased mobility of the affeeted joints. However these benefits are not consistent and in many eases the course of the disease does not appear to be materially affected. Dysphagia usually persists. In some persons the vasomotor manifestations appear to be less severe during treatment with the steroid hormones, and may be further enhanced by the addition of vasodilator drugs sueh as Priscoline or Ilidar. However the long term results have been disappointing in the majority of patients.

Surgical Procedures

Removal of calcium deposits and parathyroidectomy have not been helpful. Periarterial sympathcetomy and bilateral cervical sympathectomy have resulted in temporary improvement in a few cases.

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LUPUS ERYTHEMATOSIS

D. J. R. PETRIE, 5T7
J. A. LOWDEN, 5T7

LUPUS erythematosus is a chronic, remittent disease of unknown aetiology whieh affeets primarily the collagenous tissues. Osler's deseription of the disease is as good to-day as when it was first written.[1]

"By exudative erythema is understood a disease of unknown aetiology with polymorphic skin lesions, hypereмia, oedema, and haemorrhage—arthritis occasionally, and a variable number of visceral manifestations, of which the most important are gastro-intestinal crises, endoearditis, pericarditis, acute nephritis, and haemorrhage from the mucous surfaces. Recurrence is common and attaeks may come on month after month or even throughout a long period of years. The attacks may not be characterized by skin manifestations; the visceral symptoms may be present and to the outward view the patient may have no indication whatever of erythema exudativum."

Historical Note

In 1828 Biett[2] first deseribed the dermal lesions. Cazenave[3] eontributed the name Lupus Erythematosus in 1851. As early as 1872 Kaposi[4] recognized the syste-

mic nature of the disease, while Osler[1] in 1895 drew attention to the occurrence of the visceral lesions in the absence of skin manifestations. Additional features were recognized from time to time but it was not until 1937[5] that the principal pathological changes were associated with tissues of mesechymal origin. In 1941, Banks[6] suggested a relationship among disseminated lupus erythematosus, scleroderma, dermatomyositis and polyarteritis nodosa, as a result of which these four were grouped under the term "collagen diseases". The discovery of the LE cell phenomenon by Hargraves in 1948 marks a major contribution to the better recognition of this disease.[8] More recently attention has been drawn to a variety of other syndromes whose relationship to lupus erythematosus still remains uncertain.[9]

Incidence

The true incidence of the disease is not known. With better recognition following the introduction of the LE cell test it may be stated that it is not uncommon. It has been reported to occur more frequently than Hodgkin's disease,[10] Addison's disease,[10] acute leukemia[11] and pernicious anaemia.[11] There does not appear to be any racial immunity.[12] The greatest incidence occurs between the ages of 15 and 40 years,[13] but no age is exempt. Women appear to be more susceptible, constituting about 80-85% of reported cases.[15] In recent reports, however, an increasing number of cases are being observed in males.[14] This may be due to improved diagnostic criteria with less emphasis on the facial rash. The disease has been observed to affect more than one sibling in a family and even twins.[17] Lupus erythematosus has also been observed in families where other members have or have had rheumatoid arthritis or idiopathic thrombocytopenic purpura.[18]

Aetiology and Pathogenesis

The aetiology of LE is unknown. In the past it has been ascribed to infections with the tubercle bacillus,[30] streptococci[21] and viruses[22] but these have never been proved.[14] The high incidence of the disease in women in the childbearing age has suggested an endocrine imbalance but no such disturbance has ever been defined.[23] Similarly the occasional onset of symptoms following exposure to drugs, sera or sunlight has suggested a hypersensitivity or allergic basis for the disease. However no consistent aetiological relationship with these factors can be established and it might be best to consider them as "triggering agents" only.[14]

Dameshek and Reeves[25] have reported three patients showing either autoimmune haemolytic anaemia or idiopathic thromobocytopenic purpura in whom splenectomy was followed by overt manifestations of systemic lupus. They suggested that the intact spleen had a controlling effect on the disease and that splenectomy led to an exacerbation of lupus by removing a possible controlling mechanism.[25]

The most recent concept of the pathogenesis takes refuge in an immunochemical disturbance in which an abnormal antibody-producing mechanism may be the most important factor.[26] Ogryzlo[9] has summed up the evidence for such a reaction:

"1. Increased production of gamma globulins.

2. The frequent occurrence of biological false positive (BFP) serological tests for syphilis (STS).

3. The LE cell phenomenon.

4. The occasional demonstration of an abnormal circulating anticoagulant.

5. The occasional presence of autoantibodies for red cells.

6. The frequent sensitivity of these individuals to sunlight, blood transfusions, chemotherapeutic agents and antibiotics.

7. The more recent observation of syndromes resembling lupus erythematosus which appear to have been precipitated by hydralazine, phenylbutazone, tetanus antiserum or other agents."

Although Klemperer originally believed the primary tissue change to represent a hypersensitivity reaction,[7] in 1951 he reviewed the evidence and stressed that the true pathogenesis would not be understood until a more complete knowledge of the normal function of collagen tissue was forthcoming.[27] He suggested that fibrinoid degeneration was actually a precipitate in ground substances and not altered collagen.

Ehrich[28] in 1952 expanded on this theme and under the heading of dysgammaglobulinemia included a broad range of collagen diseases. He suggested that abnormal gamma globulins, probably released from plasma cells, circulated in the blood stream and caused a breakdown of mesenchymal tissues with the release of certain factors including acid mucopolysaccharide. This substance may then combine with alkaline protein and precipitate in the ground substance, giving the characteristic appearance of "fibrinoid degeneration".

Moore[29] has pointed out that an immuno-chemical disturbance is responsible for many of the laboratory phenomena including the BFP reaction of STS. He suggests these reactions are the result of the action of an unknown agent or antigen which injures collagen or vascular tissue. The earliest evidence of this injury is an alteration in the serum globulins in some undetermined fashion (DGG, dysgammaglobulinemia), a change which may precede any clinical signs of the disease by months or years. Thus collagen vascular disease (CVD) and especially lupus erythematosus (SLE) may be more common, more chronic, more benign and not as uniformly fatal as heretofore believed.

To-day pathologists have come to regret the use of the term "fibrinoid degeneration". It is now generally accepted that the lesion is a precipitation of protein in the mucopolysaccharide of ground substance. The precipitation occurs on the intact collagen fibrils and gives the appearance of swelling and degeneration.

Pathology and Clinical Manifestations

The pathology of lupus erythematosus is best seen in the connective tissue of the body, the commonest sites being the vessel walls and the serous membranes but any and all collagen containing organs can be involved. There are two important pathological lesions:

1. Fibrinoid degeneration, in which the normal collagen fibrils become indistinct and the ground substance appears swollen and fragmented. At the periphery of the lesion fibroblasts proliferate and there is an infiltration with mononuclear leukocytes.

2. Haematoxylin bodies which are structureless, basophilic clumps of nuclear material from degenerated cells. They are found scattered throughout the spleen, lymph nodes, lung, heart, renal glomeruli, etc. Many other lesions of a non-specific character have been described, although in some organ systems more specific lesions may be found.

Skin

The classical lesion is an erythematous eruption which begins on the bridge of the nose and spreads to involve the cheeks, eyelids and ears. It may include other portions of the face, trunk and extremities. The rash usually consists of

slightly elevated erythematous patches which are normally less than 5 mm in diameter but may be confluent. A greasy, adherent scale is frequently present. Variations of this rash include vesicles or bullae, ulcerations,[33] petechial haemorrhages[30] or telangiectatic areas.[35] Occasionally the eruption may resemble erysipelas.[36]

Histologically the lesions are nonspecific. The essential features are hyperkeratosis, keratotic plugging of hair follicles and sweat ducts, acanthosis, and lymphocytic infiltration about the vessels and skin appendages. The late results are atrophy and scarring.[32]

Subcutaneous nodules have been described which are indistinguishable from those of rheumatoid arthritis.

Cardio-vascular

A verrucous endocarditis as described by Libman and Sacks[37] occurs in less than 50% of the cases.[31] These flat, warty vegetations measure 2 to 3 mm in diameter and occur on valve leaflets, chordae, or mural endocardium. They represent sub-endocardial deposits of fibrinoid material and degenerated cells. Myocarditis is not uncommon and pericarditis may occur in 70% of cases.[31] Heart failure may also be seen.

Lesions in the small arteries and arterioles represent one of the hall marks of the disease and include a proliferative endarteritis, periarteritis or panarteritis. Fibrinoid degeneration in the vessel walls is common[38] and may sometimes be demonstrated in skeletal muscles.[39]

Musculo-skeletal

Arthralagia and arthritis were first described by Kaposi.[40] Jesser et al[18] found an incidence of 48% in 323 cases. The joint changes are indistinguishable from those of early rheumatoid arthritis, but destructive arthritis with severe deformity of the joints is rare.[15] Microscopically the synovia show an overgrowth of connective tissue with vascular changes as described above. Muscle degeneration may be comparable to that occurring in dermatomyositis.[41]

Renal

Renal manifestations as demonstrated by abnormal urinary findings are common. When renal damage is severe, hypertension may occur with uremia as a terminal event.[43] The most characteristic histological lesions are the "wire-loop glomerulus" and focal necrosis of the glomerular tuft. Churg and Grishman have attributed this to a material which has been deposited between the epithelial and endothelial basement membranes.[44] Focal necrosis probably results from vascular occlusion following an arteritis.

Others

Peritoneal involvement may be associated with anorexia, nausea, vomiting, diarrhoea or severe abdominal pain.[31] Hepatomegaly and sometimes jaundice may be observed.

Pleuritis with sterile effusions, pneumonitis and atelectasis may be found in the lungs.[45]

Personality changes, neuroses, frank psychoses, peripheral neuritis and epilepsy have been reported[38] and may result from involvement of the central nervous system.

Lymphadenopathy and splenomegaly are common.[31,46] There may be a diffuse perisplenitis with perivascular fibrosis, "onion skin lesions", affecting the small vessels of the malpighian corpuscles.[47]

Changes in the eyegrounds resemble those seen in hypertension, the most characteristic lesion being the white fluffy exudates known as cytoid bodies. They are believed to represent a degeneration of ganglia in the nerve fibre layer of the retina.[48]

Only a small proportion of patients exhibit widespread disease with all of the manifestations described above. In many instances symptoms may be confined entirely to one or two systems with evidence of more widespread involvement as the disease progresses. General malaise, fever and weight loss are common complaints. Generalized or dependent oedema may result from cardiac insufficiency or severe renal damage with accompanying albuminuria.

There seems to be little relationship between the clinical severity and the pathological findings. Fulminating cases may show few, if any, gross pathological lesions.[31] The duration of the illness would appear to be more important than the severity.[32]

Laboratory Findings

Haematological Changes

Normocytic normochromic anaemia is usual and sometimes an acquired haemolytic anaemia is seen. The latter may be associated with a positive Coomb's test or the presence of red cell agglutinins.[14] Leucopenia is almost constant. The platelets may be reduced sufficiently to produce the clinical picture of idiopathic thrombocytopenic purpura[40] which has sometimes been improved by splenectomy.[14] An abnormal circulating anti-coagulant has been responsible for the haemorrhagic disorder in a few cases.[14]

The bone marrow is hypocellular, although occasionally there are increased numbers of plasma cells. When there is an associated haemolytic anaemia, hyperplasia of the erythroid series may be present.[38]

Changes in Serum Proteins

Electrophoresis has shown an increase in the serum levels of gamma globulin, alpha-2-globulin and fibrinogen.[14] The serum albumin may be depressed. The erythrocyte sedimentation rate is almost always increased. Abnormal flocculation tests (thymol turbidity and cephalin-cholesterol flocculation) and the LE phenomenon are indicative of a disturbance of gamma globulin production.[18] Increased serum mucoproteins may be found.[50] BFP reactions are not uncommon. They tend to be of the chronic type with a low titre.[51]

Miscellaneous Lab Findings

Albuminuria and the presence of red cells and casts in the urine are common.[42] BUN estimation and renal function tests may indicate renal impairment. Non-specific abnormal ECG and EEG recordings may also be observed occasionally. Biopsy of the skin lesions or of enlarged lymph nodes may be of value in diagnosis. The presence of focal necrosis with haematoxylin bodies is presumptive evidence of SLE.[53] Gould and Daves[54] have described a constellation of radiographic findings which they consider to be characteristic of SLE.

The LE Cell Reaction

The LE cell reaction is an in vitro phenomenon which occurs characteristically in SLE. The LE factor acts upon cells causing swelling, lysis and release of the altered nuclei. This material is phagocytized by leukocytes.[55]

Six conditions are necessary to produce the reaction:

1. LE factor, a relatively heat-labile, immunologically distinct component of the gamma globulins. It causes depolymerization of the DNA of nuclear material.[52]

2. Nucleoprotein on which the LE factor can act. This is provided by normal leukocytes.

3. Phagocytic leukocytes to engulf the lysed material. This is probably a normal response of leukocytes to foreign ma-

terial.[55] Most of the phagocytosis is done by the neutrophils.

4. The temperature must be 22-37°C.

5. A time interval of 30-120 minutes to allow nuclear degeneration to occur, the period depending on the intensity of the reaction.

6. An activating factor has been suggested by some authors to account for the fact that the reaction does not normally occur in vivo. This activator may be the product of platelet breakdown or some other coagulation mechanism. The in vitro development of the LE cells, however, may be enhanced by the presence of non-viable leukocytes which are not usually found in vivo.[52]

The principle involved in the various procedures for demonstrating the phenomenon is generally the same. The patient's serum is brought into contact with leukocytes for a specified period of time. The leukocytes are then concentrated, smeared, stained and examined microscopically. As some patients may exhibit a negative test by one procedure and later be positive on another, it is usually preferable to perform several tests.[12]

Three significant structures are seen.

1. Globs.[15] Extracellular, amorphous, globular masses of degenerated nuclear material. These may be seen in various stages of phagocytosis.

2. The LE cell. This characteristic structure is necessary for a positive diagnosis. It is a leukocyte (usually a polymorph) distended by a large globular, amorphous inclusion body which stains slightly less basophilic than the nucleus of the neutrophil. The inclusion bodies represent the above-mentioned globs of nuclear material which have been phagocytosed, and may be identical with the haematoxylin bodies seen in the tissues of autopsy or biopsy material.[52]

3. The Rosette. This is a mass of nuclear material surrounded by a collar of neutrophils. Dubois[12] ordinarily considers a test positive when two LE cells are seen per 1,000 leukocytes.

Because of the difficulty in establishing a definite diagnosis, the absolute specificity of the LE phenomenon remains uncertain. It is not possible to demonstrate LE cells in every case of SLE,[12] nor is there any correlation between the severity of the disease and the number of LE cells present.[52, 26] (Moore and Lutz[26] believe that the phenomenon is a late development in SLE and that other manifestations may be present for long periods before a positive test is demonstrable.) The test has occasionally been reported positive in other disease states,[55] although Dubois, in reviewing a long series of tests, states that "false positives do not occur, with the possible exception of the Hydralazine syndrome, which may be a chemical induction of SLE".[12] Harvey et al.[14] support this view. While the LE phenomenon occurs most characteristically in SLE, its occasional demonstration in other disease states suggests that it may not be absolutely specific for SLE.

Diagnosis

The disease may present varied clinical manifestations, making early diagnosis difficult. There may be a history of vague illness or recurring infection. The patient may have been treated for presumed latent syphilis. Severe emotional disturbance or even psychotic episodes are common, while some patients have a long history of idiopathic epilepsy. Chronic ill health with weight loss, fatigue, etc. may be followed by a proven diagnosis of SLE. Rheumatic fever, rheumatoid arthritis, glomerulonephritis and Raynaud's phenomenon are frequently recorded in the past history. Jessar et al.[18] found that 11% of their series of 323 patients had Raynaud's

phenomenon at some time prior to their diagnosis.

Cardiac, pulmonary, renal, neurological and gastro-intestinal manifestations are frequently encountered. Dermatalogical conditions, blood dyscrasias and pyrexia of unknown origin may be given as the cause of the patient's distress. Indeed the manifestations run the entire gamut of internal medicine but SLE should not be allowed to become a "catch-all" term for any puzzling malady with bizarre clinical or anatomical features.

A group of syndromes which may be related to SLE have been described by Ogryzlo.[9] The conditions occasionally show the LE phenomenon and bear a superficial resemblance to SLE but differ in their clinical picture, natural course and prognosis. The syndromes are:

(1) Diffuse Systemic Rheumatoid Disease.

(2) Chronic Hepatitis with cirrhosis.

(3) Hydralazine Syndrome.

(4) Penicillin and Phenylbutazone Reactions.

Classification

There is no good classification of lupus erythematosus, although cases may arbitrarily be grouped according to their severity with no fixed line of demarcation between them.[59] The disease tends to vary in its course and can become extremely acute in a short period.

1. Chronic Discoid Lupus Erythematosus (CDLE). The patient has the classical indurated scaling erythematous lesions which are confined largely to the face.

2. Chronic Systemic Lupus Erythematosus (CSLE). As well as the lesions on the face there are typical discoid lesions elsewhere on the body. Occasional flare-ups of systemic involvement occur (fever, arthralgia, abnormal liver function tests, etc.). The LE test remains negative.

3. Subacute Systemic Lupus Erythematosus (SSLE). A more virulent form with severe exacerbations. LE cells may sometimes be found. The skin lesions resemble the chronic discoid or acute erythematous type.

4. Acute Systemic Lupus Erythematosus (ASLE). A fulminating course, a positive LE cell test and a butterfly rash characterize this form which tends not to remit.

The Relationship between Chronic Discoid and SLE

Internists and dermatologists cannot agree on the question of such a relationship. Baehr states that there is no relationship.[60] Montgomery on the other hand says that one-third of his cases of SLE developed from CDLE.[61] Pillsbury refutes this, saying that in such cases the original diagnosis was in error. If the diagnosis of CDLE is made with certainty "the patient may be given rather firm assurance that the process is of no great general medical significance."[62]

Wilson and Jordan point out that histologically all gradations between chronic discoid and acute systemic lupus may present similar lesions.[63] The microscopic appearance varies with the duration of the lesions. "Clinical evidence of relationship is supported by experimental evidence which indicates that fundamentally similar alterations in peripheral blood flow, serum protein electrophoretic patterns and polysaccharide materials in the corium (as shown by the McManus stain) occur in the chronic localized and the disseminated forms of the disease. This evidence also suggests that chronic discoid lupus erythematosus may be a systemic disease from its inception in all cases."[63]

Any of the systemic abnormalities can

exist in CLE with the exception of the LE cell test,[11] although Dubois states that on rare occasions patients with localized CDLE may be found to have a positive LE cell test.[13] A high percentage of patients with CDLE have false positive STS.[64] Careful investigation of patients with the discoid form reveals a high incidence [96% of one group of 41 patients with CDLE[59]] of fatigue, malaise, arthralgia, slight evening fever, albuminuria and leucopenia.[24] Differences between systemic and discoid LE in response to various therapeutic agents are not as marked as previously believed.[65] A case has been reported in which a newborn infant had an eruption clinically and histologically consistent with a diagnosis of CDLE. The mother developed acute SLE eleven months post-partum.[66]

The evidence seems to favour a unitarian theory quite impressively. CDLE can and does undergo transition to the acute or subacute forms, especially when such factors as actinic rays, trauma, or toxic drugs have been active.[63, 65] It is important to accept this concept and to avoid dismissing CDLE as an inconsequential condition.

Treatment

The problem is that of a chronic illness of unknown aetiology which may show a tendency toward remission even without treatment. Many therapeutic agents have been tried without success in the past and even now those currently used are non-specific, providing symptomatic relief only.

Treatment of CDLE

Patients with CDLE are not systemically ill. The disease may progress for years with remissions and exacerbations, in some instances leading to severe disfigurement regardless of the type of treatment. Anti-malarial agents, first used by Payne in 1894,[62] appear to have a beneficial effect on the cutaneous lesions. A number of observers[57, 62] have reported good results with quinacrine (Atabrine, Mepacrine). Toxic effects include a yellowish discoloration of the skin, gastro-intestinal disturbances, headache, depression, dermatitis and hepatitis. More recently, chloroquine has been shown to have less severe toxic effects.

The patients should be cautioned against exposure to actinic rays, trauma, potentially toxic drugs, infections and the indiscriminate removal of foci of infection.[65] They should be examined periodically with regard to general health, ESR, STS, haemoglobin, white blood count and urinalysis. Ultra-violet light and X-rays are definitely contra-indicated.

Treatment of SLE

1. *General Management*

Patients who are inadvertently discovered to be BFP reactors and have a positive LE test but who are otherwise asymptomatic require no treatment. In the presence of a mild arthritis, salicylates in moderate doses (4-5 gms. daily) will often control symptoms. In more active cases a period of bed rest is indicated. Anti-malarial drugs may be tried in the less severe cases, especially if skin lesions are present but, if the patient is critically ill, steroid therapy should not be delayed.[12]

2. *Aspirin*

Aspirin will provide symptomatic improvement in most patients with a decrease in temperature and an improved sense of well-being. It may also reduce the requirements for anti-malarials and steroids.[14]

3. *Anti-malarials*

A varicty of the anti-malarial drugs have been advocated, either singly or in combinations. Quinacrine has been shown to inhibit the LE phcnomenon in vitro, indicating some rationalc for its use. Patients with CDLE and less active SLE tend to respond more favorably than severely ill patients.[57] Because the skin becomes yellow with quinacrine, chloraquine is now more widely used. The initial dose of 750 mgs. daily is continued for several weeks until a response is obtained, when it is reduced to a maintenance level of 250-500 mgs. Mild toxic effects from these drugs may necessitate further reduction in the dose while psychosis or dermatitis prohibit their use. They tend to have a cumulative effect and toxic signs may not appear for four to six weeks.

4. *Steroids*

Steroid therapy constitutes one of the greatest advances in the treatment of SLE. It should be used for all critically ill patients and benefits 90% of those so treated.[12] Fever is reduced within 48 hours and arthralgia disappears within a week in most cases. Most other physical signs improve more gradually. LE cells may become fewer in number and more difficult to demonstrate.[54] The ESR falls but the BFP persists in most cases. Renal manifestations and hypertension are influenced only if these have been recent in their appearance.

Treatment may be initiated with ACTH of the long acting type, given intramuscularly in a dosc of 40-80 units per day. As symptoms improve the dose may be reduced gradually to a maintenance level of 20-30 units per day. The convenience of oral administration has made cortisone and hydrocortisone more popular than ACTH. Initial doses vary from 100 to 300 mgs. daily, with a gradual reduction to a maintenance level of 50-75 mgs. per day as symptoms improve. More recently prednisone and prednisolone have gained popularity because of their decreased tendency to salt retention. The usual initial dose of either hormone is 30 mgs. daily with a gradual reduction to a maintenance dose of 10-20 mgs. per day. With all of these hormonal agents, varying degrees of salt restriction may be necessary depending on the age and cardiovascular-renal status of the patient and the choice of hormone will be governed in a large degree by these factors.[12] Contraindications to hormonal therapy are essentially the same as in other disease states.

The initial doses of steroids will vary with the severity of the illness and should be planned so as to dominate the disease manifestations quickly.[56] When the fever and other systemic manifestations have been controlled for a period of one or two weeks, the dose may be reduced by about 10% at intervals of one to four weeks, depending on the response after each reduction. Frequently it is not possible to suppress all of the manifestations with doses that will not give rise to undesirable side effects. In the presence of progressive disease or fulminating crises, larger doses with their accompanying risk of complications may be justified but should not be continued longer than is necessary. Sudden withdrawal of treatment or too rapid reduction of the dose of hormone may be followed by severe relapse.

5. *Nitrogen Mustard*

Nitrogen mustard, which is known to inhibit antibody production, has recently been reported to be of value in the treatment of patients with the nephrotic

manifestations of lupus when they fail to respond to hormone therapy, low salt diet and mercurials.[56] A marked diuresis may occur within a few days to two weeks. The therapy is of no value when no renal involvement is present.

6. *Adjuvant Therapy*

Patients with SLE may require analgesics for pain, transfusions for anaemia, antibiotics for infection, digitalis and salt restriction for cardiac failure and mercurial diuretics for oedema, but these drugs should not be used unless they are definitely indicated.

Clinical Course and Prognosis

The clinical course of the disease is often characterized by remissions and exacerbations of varying duration. A prolonged course over many years is common but fulminating cases do occur. Spontaneous remissions may last for one to four years and longer.

Due to the minor nature of the initial manifestations in many instances it is difficult to determine the exact onset of the disease. Merril and Schulman[69] estimate the interval between onset and diagnosis to vary from one to 35 years (ave. 4.9 yrs.). About 50% of patients survive four years or longer after diagnosis. Moore and Lutz[26] have found that the laboratory changes (chiefly BFP-STS, gamma globulin changes, certain flocculation tests) may be present for years in the absence of detectable clinical disease. They have shown also that the chronic BFP reactors frequently develop a disease syndrome in later years, which conforms to that of SLE. This concept of a prolonged latent period during which the patient may be relatively asymptomatic, is in contrast to the usual textbook picture of the disease.

Summary

1. Lupus erythematosus is a chronic disease characterized by frequent remissions and exacerbations, although a proportion of the cases may run a fulminating and fatal course.

2. The disease appears to be commoner than heretofore suspected.

3. The important pathological lesions are found in the collagen tissues of the blood vessels, serous membranes and viscera.

4. Diagnosis is made on the basis of the history and physical examination and supported by the laboratory findings, of which the most important is the LE cell test.

5. It seems probable that chronic discoid lupus erythematosus and the more severe systemic form are variants of the same disease.

6. Treatment measures include bed rest, salicylates, anti-malarial drugs, adrenal steroid hormones, nitrogen mustard and symptomatic care.

7. At the present time it is difficult to determine whether the addition of these newer chemotherapeutic and hormonal agents has altered the natural course of the disease in any fundamental way, but it is generally believed that they have reduced the overall morbidity and mortality rate.

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POLYARTERITIS NODOSA

D. GLICK, B.A., 5T7
S. RABINOVICH, 5T7
G. I. URBACH, B.A., 5T8

POLYARTERITIS may be described as a non-specific, non-suppurative, inflammatory disease affecting small or medium-sized arteries and arterioles. There is current feeling, however, that all of the conditions in which there are vascular lesions characterized by inflammatory reaction and fibrinoid necrosis of the type that occurs in polyarteritis nodosa, do not constitute a single disease entity. This view is based on certain differences in the morphology and distribution of the lesions in different cases, which have been observed to induce similar lesions in animals. For this reason descriptions of the disease are to be found under a variety of synonyms, including, periarteritis nodosa, panarteritis, hypersensitivity or allergic angitis, necrotizing angitis and others. This situation has added confusion to our understanding of the disorder. The vascular lesions are usually segmental in their distribution, with the intervening portion being spared. The involved areas may be enlarged to form palpable nodules along the course of the vessel, hence the name 'nodosa'. If the wall has been weakened actual aneurysmal dilatations may be seen. Nodular lesions sufficiently large to be seen by the naked eye, or palpated by the fingers are not common and occur in less than 10% of the cases.

History

Von Rokitansky is credited with the first description of the clinical and autopsy findings in this disease, in 1852. The histological changes were later described by Kussmaul and Maier in a detailed treatise published in 1866. They gave it the name Periarteritis Nodosa and described it as a progressive, recurring, necrotizing, inflammatory panarteritis, affecting chiefly small and medium-sized arteries, with regional symptoms depending on the specific organs involved and exhibiting symptoms of systemic infection. The name Polyarteritis Nodosa was suggested by Ferrari in 1903. He stressed the fact that all coats of the vessel wall were usually affected. The disease is relatively uncommon and has frequently gone unrecognized until autopsy has been performed.

Aetiology and Pathogenesis

The specific cause of the disease, if there is a single cause, remains unknown. However, in this disease, more than in any other member of the collagen group of diseases, hypersensitivity has been known to play a major role. Many observations, both clinical and experimental, point to the probability that the vascular lesions of polyarteritis nodosa are manifestations of hypersensitivity.

In 1934, Kline and Young[1] suggested that the arterial lesions represented allergic manifestations in highly sensitized individuals, some of the lesions being reversible, while others were irreversible, degenerative and necrotic. In 1937, Clark and Kaplan[2] described vascular lesions in the hearts and testes of two patients who died of serum sickness, resembling those of polyarteritis.

[*Compiled from papers presented before the AOA.]

Typical lesions of polyarteritis have been produced experimentally in animals by the intravenous injection of horse serum and with sulphonamides. Most significant in this respect has been the work of Arnold Rich[3] who provided strong experimental as well as clinical evidence to show that anaphylactic hypersensitivity to a variety of agents may be associated with identical vascular lesions.

Whether there has been an actual increase in polyarteritis in recent years with the introduction of newer chemotherapeutic agents, is open to question. However, a review of 76 autopsies in 1946,[4] reported significant histopathological changes which suggested an individual susceptibility to sulphonamides, even though the drug was administered to some of the patients only a few days before death. Other authors have reported many instances of polyarteritis appearing after the administration of, or contact with, other substances among which are included, foreign serum, vaccines, penicillin, poison oak, mercury, arsenic, iodine, dilantin, thiouracil and even cortisone and ACTH. Further support for this thesis comes from the frequent association of bronchial asthma and other allergic manifestations variously quoted as occurring in 12–25% of cases. Similarly the demonstration of eosinophilia in a large proportion of cases lends additional support to this view.

An infectious origin for polyarteritis has been proposed by some investigators who have observed infectious prodromata in a number of patients. These have included acute tonsillitis, scarlet fever, rheumatic fever, influenza, pneumonia, typhoid fever, malaria and syphilis.

The frequent association of hypertension and polyarteritis is of considerable interest. In 1951, Wilens and Glynn reviewed 94 cases,[5] 60% of whom were hypertensive. The hypertension preceded the symptoms of generalized vascular disease in 10% of the patients, while in another 37% it appeared concurrent with the onset of symptoms. It was also noted that the incidence of allergic manifestations was lower in the hypertensive group. The data suggested that polyarteritis developed more frequently in hypertensive individuals even in the absence of an allergic background.

On the experimental side, polyarteritis has been induced in rats by a combination of unilateral nephrectomy together with the administration of desoxycorticosterone acetate and a high salt intake and also by the artificial production of renal infarction, by wrapping the kidney in silk.

Incidence

While polyarteritis is an uncommon disease it is far from being a clinical oddity. Accurate figures concerning its incidence cannot be given but it is probable that the apparent increase in the number of cases reported in recent years is due to a greater awareness of the disease together with improved methods of diagnosis. A positive diagnosis can only be made by the demonstration of the typical lesions in the tissues obtained at biopsy or postmortem examination.

Males are predominately affected with a sex ratio of 3:1. The disease has its highest incidence between the ages of 20 and 50, although instances in the very young as well as the very old have been reported. A familial incidence has not been reported although other manifestations of hypersensitivity may occur. No race is exempt.

Clinical Features

Few diseases exhibit the protean manifestations which are commonly encountered in polyarteritis nodosa. There

is no characteristic group of symptoms and the clinical manifestations may be extremely variable. The onset of the disease may be acute but more often the symptoms begin insidiously. The patient may complain of a low-grade fever, weight loss, anorexia, weakness, abdominal pain, neurological disturbances or visual changes. Chills are unusual. More specific symptoms are usually referable to the organs involved and will be discussed separately, although they may develop concomitantly.

Kidneys

The vessels of the kidneys are affected in most cases and may give rise to the clinical picture of glomerulonephritis or renal infarction. There may be pain in the lumbar region, and varying degrees of urinary suppression. Hypertension is common in such cases with renal failure in the terminal stages. Retinopathy, either on the basis of hypertension or uraemia, may be observed.

Heart

Vascular lesions may occur in the pericardium and myocardium giving rise to a pericarditis which may be haemorrhagic in nature, a myocarditis with cardiac insufficiency, or sometimes frank coronary occlusion. The electrocardiogram is frequently abnormal.

Gastrointestinal Tract

Involvement of the vessels in the mesentery and bowel wall may give rise to abdominal pain, tenderness, nausea, vomiting, distention, diarrhoea or frank melena. Not infrequently these patients may present with symptoms of acute appendicitis, cholecystitis, pancreatitis or intestinal obstruction.

Lungs

Complaints referable to the lungs are apt to be minimal except in those patients with a history of bronchial asthma. Chronic cough, blood-stained sputum and pleuritic pain are not unusual. Pleural effusion sometimes associated with a transient pneumonitis or more rarely granulomatous lesion in the lungs may be secondary to the underlying vascular changes.

Nervous System

Neurological manifestations may include, personality changes, headache, dizziness, visual impairment, convulsions, peripheral neuritis, with anaesthesias, paraesthesias or even motor paralysis. Apoplexy may be a terminal event.

Muscles and Joints

Muscle tenderness may occur secondary to involvement of the nerve supply or related to the vascular lesions in the muscles. Objective signs of joint disease occur in some patients with arthralgia or joint swelling and local tenderness, resembling that of rheumatoid arthritis.

Skin

Approximately 25% of patients with polyarteritis show cutaneous manifestations. These include petechial haemorrhages, erythema multiforme, urticaria, bullae or areas of necrotic ulceration. Transient subcutaneous nodules, indicating segments of involved vessels may be found in about 10% of cases.

Laboratory Findings

A mild normochromic normocytic anaemia may be present. Leucocytosis of varying degree is a frequent occurrence although the cell count may be normal. In extreme instances the WBC may reach as high as 60,000 per cu.mm. A transient or persistent eosinophilia is common and may be as high as 75 to 90% of the differential count. The sedimentation rate is almost invariably elevated. Urinalysis may reveal albuminuria, red and white blood cells and casts. The serum protein may show a reversal of the normal pattern with reduction of the albumin fraction and an

increase in the globulin, particularly the gamma globulin.

Diagnosis

Polyarteritis should be considered in any obscure illness in which there is evidence of involvement of multiple organ systems. The occurrence of fever associated with hypertension, haematuria, peripheral neuropathy, abdominal symptoms and eosinophilia should be viewed with suspicion. Confirmation of the diagnosis rests on the demonstration of the vascular lesions in biopsy material taken from the skin, skeletal muscle or other organs.

Clinical Course

The clinical course of polyarteritis nodosa is extremely variable. Fulminating cases may progress to a fatal termination within four to twelve months of the onset of symptoms. There are reports of patients living in apparent good health for many years in whom the diagnosis has been confirmed by biopsy but in these instances the arteritis has usually been localized to a relatively small area or non-vital organ. Involvement of the central nervous, renal, cardiovascular or respiratory systems should be interpreted as indicating a more serious prognosis.

Treatment

The treatment of polyarteritis may be divided into symptomatic and prophylactic.

Symptomatic treatment involves such measures as high caloric diets, opiates for the relief of severe pain, and blood transfusions in the presence of severe anemia. The only agents which have been shown to exert significant suppressive action on the inflammatory process are adrenocorticotrophic hormone and the cortico-steroids. A careful search should always be made for a possible offending antigen. Antibiotics may be indicated in the presence of bacterial infection but have no effect on the vascular lesions. As part of the prophylactic aspects of this disease the unnecessary administration of antibiotics and chaemotherapeutic agents should be avoided in patients with a known history of drug hypersensitivity.

Hormone Therapy

Beneficial results have been reported with the administration of a variety of hormone agents including ACTH, cortisone, hydrocortisone, prednisone and prednisolone. However the number of cases responding to these is discouragingly small. In many cases the tendency is towards the progression of the disease with only symptomatic relief. More complete remissions with suppression of clinical symptoms, inhibition of the progression of vascular lesions and microscopic evidence of their healing have been reported in isolated instances. In a few patients the remissions may be prolonged but more often the disease relapses when the drug is discontinued. Under such circumstances hormonal therapy must be prolonged for an indefinite period.

Many authors have cautioned against the use of steroid hormones in polyarteritis. Healing of the vascular lesions tends to be followed by extensive scarring and eventual occlusion of vessels. In general the treatment of polyarteritis with steroids has been disappointing. The overall mortality rate remains high, approximately 75% of all cases.

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RHEUMATOID ARTHRITIS

M. BERGER, 5T7

RHEUMATOID arthritis, generally classified as one of the collagen diseases, is a medical problem of considerable magnitude and complexity. It is one of the major causes of chronic disability in Canada. It strikes all age groups, spares no economic or social group. In its management the physician, physical therapist, surgeon, psychiatrist and social worker must act as a team to restore the patient to an active and useful role in the community. Since it is a disease or syndrome of unknown etiology, subject to unpredictable remissions and exacerbations, the physician may become discouraged, believing that little can be offered to the patient. This leads to a disheartened patient, deprived of the reassurance and hope which is so important a part of the treatment. However fully 50% to 75% of patients can be restored to useful living with early diagnosis and active treatment.

The following is a summary of the present state of knowledge of this syndrome:

Definition

Rheumatoid arthritis is a systemic disease in which inflammatory changes in articular and periarticular structures predominate. These changes may progress to severe destruction and ankylosis of the joint. The course is one of chronicity with spontaneous remissions and exacerbations, making evaluation of therapy difficult.

Etiology

The Etiology and pathogenesis are unknown. The introduction of ACTH and the adrenal cortical hormones as potent anti-rheumatic agents, has revived the concept that rheumatoid arthritis may be related to some abnormality of endocrine balance, but in particular steroid metabolism. This view found support in the frequent observation of remissions occurring during pregnancy or jaundice, both of which are associated with an increased level of circulating steroids. Against this concept is the fact that there is no increased incidence of the disease in patients with Addison's disease. The 17-keto steroid and glucocorticoid excretions in the urine in rheumatoid arthritis are normal or only slightly lowered. Furthermore, the doses of ACTH or cortisone necessary to induce remissions cannot be regarded as replacement therapy but rather pharmacological doses which produce a state of hyper-adrenalism. Finally, there is accumulating evidence that these hormones do not arrest the underlying disease process but merely retard its progress.

No specific infective agent has been demonstrated in rheumatoid arthritis. The role of focal infection as the cause of the disease, which was popular after the turn of the century has largely been abandoned. The elevated titre of agglutinins to hemolytic streptococci which can be demonstrated in a large proportion of the patients is probably the result of qualitative changes in the serum proteins, rather than an indication of streptococcal infection. In this respect it is comparable to other agglutination reactions in this disease.

Psychogenic factors are important in precipitating exacerbations or relapses, but no significant relationship has been shown to exist between psychic trauma and the onset of the disease.

There is evidenee that the underlying proeess may represent a disturbanee of the mueopolysaeeharide-protein complexes whieh make up the ground substanee of eonneetive tissue. The synovial fluid shows inereased quantities of hyaluronie aeid existing in the depolymerized form. It has been suggested that the ehanges may be explained on the basis of hypersensitivity with autosensitization to a tissue eomponent, but faetual evidence to support this hypothesis is laeking.

Although many other theories of the eause of rheumatoid arthritis have been proposed, none are aeeeptable.

Pathology

Edema, proliferation of synovia, joint effusion and peri-artieular swelling represent the earlier ehanges. At this stage the disease may still be reversible. As the disease progresses the synovial membrane proliferates to form a pannus whieh overlies the articular surfaees and eauses erosion of the cartilage. Subehondral bone is then resorbed by proliferating granulation tissue. The X-ray ehanges, whieh may not be reeognized for some months, show irregularity of artieular surfaee, narrowing of the joint spaee and osteoporosis. Fibrous ankylosis between the joint surfaces is the natural eonsequenee of these changes, and may result in permanent limitation of joint mobility, with solid boney ankylosis in the final stages. Musele spasm and atrophy of opposing musele groups play a major role in the produetion of pain and eontractures. Rheumatie arthritis is a systemie disease and may be asso-eiated with involvement of multiple organ systems. Myositis is a frequent finding and sometimes an arteritis and peripheral neuritis, chronie valvular lesions of the heart, similar to those found in rheumatic fever, are seen not infrequently. Interestingly enough, amyloidosis occurs in about 20% of eases eoming to autopsy. In this respect it is comparable to the assoeiation of amyloidosis with many ehronie infeetions. The subcutaneous rheumatoid nodules represent the hall mark of rheumatoid arthritis, being present in 20% of eases. They are found most eommonly on the oleeranon proeess just distal to the elbow, but may oeeur at other pressure sites. The lesion represents a granulomatous proeess, exhibiting a eentral area of necrosis, surrounded by a palisaded layer of fibroblasts and granulation tissue.

Laboratory Findings

A moderate secondary anemia, of the normoehromie normoeytie type is common in aetive rheumatoid arthritis. The leucoeyte count is usually normal or increased, but may oeeasionally be dereased in those eases assoeiated with generalized lymphadenopathy and splenomegale.

Agglutination of sheep red blood cells, sensitized with rabbit antisheep amboeepter, by sera of patients with rheumatoid arthritis is present in higher titres than normal sera. A recent modifieation of the hemagglutination test using the euglobulin fraction of plasma, is highly sensitive and may prove a valuable diagnostie tool. The serum proteins are altered in most cases, with a decrease in the serum albumin and an increase in the gamma globulin fraetion. The plasma fibrinogin is usually inereased and aeeounts for the inereased sedimentation rate during the active stages.

Epidemiology

Rheumatoid arthritis is found among the families of affeeted patients five to six times more frequently than in the general population, indieating a distinet familial tendeney and possibly genetic suseeptibility. The disease has its maxi-

mum incidence between the third and fourth decade. Females are more frequently affected, in the ratio of three to two. Juvenile rheumatoid arthritis, beginning most frequently in the third and fourth year, makes up about 5% of the total cases. The temperate zone and particularly regions with a cold, damp climate appear to have a higher incidence. All classes are affected although the lower economic groups are more seriously involved.

Psychic factors play an important role in the course of the disease as well as modifying the effect of therapy. It is of some interest to note that the disease is much less common among the psychotic population of mental institutions.

Clinical Features

The course may vary from the acute febrile type with rapid onset of deformities to the chronic insidious and indolent form. The prodromata may include fatigue, anorexia, weight-loss, early morning joint stiffness which is relieved as the day progresses and excessive perspiration with moist palms and soles. In most cases the disease begins with involvement of the small joints of the hand, notably the proximal interphalangeal joints and metacarpophalangeal joints. However any joint may be affected. Associated with the joint changes are muscle atrophy and spasm. Complete or partial remissions are common, but the disease may progress with infrequent remissions for many years until it eventually burns itself out. The affected joints are swollen in a fusiform fashion, with pain, tenderness and increased heat, and may be associated with the presence of free fluid. Usually the joints are symmetrically involved, although this is not always the case.

Freely movable, subcutaneous nodules on the extensor surfaces of the forearms are commonly present. Unlike those that occasionally accompany rheumatic fever, these usually persist for months or years. Uveitis and iritis may occur but are not as common in rheumatoid arthritis as in Marie-Strümpell spondylitis. Pericarditis or pleurisy with effusion may complicate the picture in those patients with severe systemic involvement. The L.E. phenomenon has been reported to be present in 7-15% of cases. In such patients, the distinction from other members of the collagen diseases may be exceedingly difficult.

Diagnosis: Proposed Diagnostic Criteria for Rheumatoid Arthritis[2]

A. Definite Rheumatoid Arthritis

Diagnosis requires five of the following criteria and total duration of joint symptoms must be at least six weeks.

1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint.
3. Soft tissue swelling in at least one joint.
4. Swelling in at least one other joint, the interval between the two incidents not more than three months.
5. Symmetrical joint swelling with simultaneous involvement of the same joint on each side. Bilateral involvement of the midphalangeal, metacarpophalangeal and metatarso-phalangeal joints is acceptable without absolute symmetry.
6. Subcutaneous nodules on the extensor surfaces.
7. Typical rheumatoid X-ray changes.
8. Positive sheep cell agglutination.
9. Poor mucin precipitate from synovial fluid.
10. Typical histological synovial changes.

B. Probable Rheumatoid Arthritis

Requires three of the above criteria and duration of four weeks without the appearance of any exclusions.

C. Possible Rheumatoid Arthritis

Requires two of the above eriteria and duration of three weeks without the appearanee of any exelusions.

Exclusions: exelude the diagnosis of "probable or Possible" rheumatoid arthritis by their presenee.

1. Butterfly rash of Lupus Erythematosis; high coneentration of LE eells.

2. Pieture of seleroderma, dermatomyositis, gout, periarteritis nodosa, shoulder and hand syndrome, rheumatic fever or Reiter's syndrome.

3. Aeute viral and bacterial arthritides.

4. Pulmonary osteoarthropathy with elubbing of fingers, or neuro-arthropathy.

5. Leukemia, lymphomas, multiple myeloma, sareoidosis, erythema nodosum, and hemogentisie aeid in the urine.

The main purpose in outlining these eriteria for diagnosis, has been to ensure greater uniformity in reporting the results of studies on the elinieal and pathologieal manifestations of the disease, as well as in evaluating the results of different forms of therapy. The eriteria are not designed to be absolute, but it is hoped that by eonfining reported observations to those eases whieh conform to "definite rheumatoid arthritis", we may gradually gain a better understanding of the prevalenee, natural eourse, response to treatment and other features of the disease.

Treatment

There is no speeifie therapy. Onee the diagnosis has been firmly established, the patient should be told of the nature of the disease but should be reassured and given an optimistie outlook. The patient is eneouraged to partieipate in his own therapy. Sinee psyehie faetors may preeipitate an exaeerbation and the disease may be seeondarily assoeiated with great mental distress, the art of medicine is as important as its physieal methods. The doctor and his relationship to the patient are often more important than the medieation he is dispensing. The aim of therapy during the aeute attack is to reduee the aetivity of the disease until it subsides naturally.

A. Rest:

Rest of the body and of the affected joints is important. This is aehieved by bed rest, splinting by light weight splints and by psyehie rest, a positive therapeutie program and an aetive plan for the patient, possibly making use of a social worker. To reduce and prevent deformity and alleviate pain and spasm, the methods of physieal medieine are utilized. "Severe systemie illness with acute joint inflammation may respond dramatically during continuous immobilization of the joint involved."[2]

The amount of bed rest will vary with the aetivity of the disease and involvement of the weight-bearing joints. Therefore rest will range from complete to increased rest, that is ten hours of sleep with noon-hour naps. Fracture-boards are plaeed under the mattress to prevent the development of a kyphosis and flexion contractures of the knee.

Early aetivity of the joints is important, for experience has shown that late mobilization leads to deformity. The joints are put through their full range of movement by graduated steps, starting with ten minutes of exercise twice a day and progressing to about twelve times per day. The eriterion of too rapid progression is indieated by an inerease in joint pain whieh persists more than one hour after the eompletion of the exereises. The antigravity museles, the hamstrings and quadrieeps become grossly weakened in the bed-ridden patient. The strength of these joint-stabilizing museles is preserved by tension exereises.

B. Diet

High protein diet with adequate calories to maintain weight. A well balanced diet should not require vitamin supplements, although these may be indicated in obese patients on low calorie diets for weight reduction.

C. Reduction of Pain and Spasm

1. Analgesics: Salicylates are the drugs of choice, the most popular form being aspirin.
2. Joint rest.
3. Application of heat; infra red, paraffin wax baths, whirlpool baths, etc.

D. Local Joint Therapy

Hydrocortisone, injected intra-articularly in severely affected joints may enhance the effect of the physiotherapy program.

E. Treatment of the Anemia

Typically the blood picture is a normocytic, normochromic anemia. The metabolic error is not iron deficiency, for the total body iron is not reduced. It is best explained on the basis of a defective marrow erythropoiesis accompanied by increased red cell destruction. The success claimed by some investigators using iron may have been due to a complicating iron deficiency anemia or a coincident remission of the disease. Except in very severe anemia, whole blood transfusions are rarely indicated, because of the inherent danger of serum hepatitis and short lasting effect, since exoginous red cells are as rapidly broken down.

F. Steroids

The remission-inducing potential of the various steroid hormones is temporary and persists only as long as the therapy is continued. Because exacerbations occur upon their discontinuation, their undesirable side-effects and prohibitive cost, this group of agents should be used as a second line of attack, and should be prescribed only after more conservative measures have been shown to be ineffective. Even then, the addition of these hormones must be regarded merely as an adjunct to the general measures outlined above.

G. Butazolidin

Phenylbutazone (Butazolidin), an analgesic agent with anti-rheumatic properties, is associated with some risk of toxicity, including dermatitis, agranulocytosis and nephritis. It is not as effective as cortisone, and related steroid hormones in its anti-inflammatory action, but may be very effective in relieving pain.

H. Chrysotherapy—Gold Salts

No agreement exists concerning the use of gold compounds in the treatment of rheumatoid arthritis, although a significant number of patients with well documented disease have been observed to go into partial remission following a course of gold therapy. This is especially true in the early stages. Toxic reactions occur in a large proportion of cases, and may affect the skin, hematopoietic system, kidneys, liver and other organs.

J. Antimalarial drugs

The use of various antimalarial drugs has recently been advocated in the treatment of rheumatoid arthritis, particularly in milder cases. Quinacrine (Atabrine) and chloroquine (Aralen) have both been used in various trials, with preference for the latter because of its lower toxicity. However, these drugs cannot be regarded as potent anti-rheumatic agents.

K. Surgery

Orthopedic surgical procedures may have to be utilized for the correction of deformities when the disease has become more or less quiescent. However, it is

important to remember that deformities are often the result of improper care and inadequate education of the patient. They can be prevented in most patients by careful supervision and the intelligent application of physical measures.

Some of the useful procedures

a) Excision arthroplasty: Ends of bones are excised and healing is allowed to occur with fibrous ankylosis. This can result in the preservation of useful movement in a non-weight-bearing joint.

b) Replacement Arthroplasty: Joint surface is excised and replaced by prostheses resembling the normal surface. Such procedures are suitable for weight-bearing joints like the hip.

c) Arthrodesis, (fusion): This is used to control pain in weight-bearing joints with little residual movement, and results in a stable painless limb.

d) Tenotomy and Capsulotomy: The fibrosed tissue of the capsule and periarticular tissue is divided in order to allow greater range of movement and correct flexion contractures.

e) Osteotomy: Bone ends are reconstructed so that the long axis of adjacent bones are in line during extension. The procedure may be used as an alternative to (a).

Prognosis

The prognosis depends on the severity of the disease and the stage at which active treatment is started.

In one series[3], of 256 patients treated conservatively, the data compiled after ten years was: 53% improved; 13% same; 30% worse.

Asymmetric joint involvement occurring in males under forty years of age, with a history of less than one year's duration and minimal symptoms prior to diagnosis, generally have a good prognosis.

Relapses are unpredictable, and occur in about 30% of cases.

DERMATOMYOSITIS (Polymyositis)

N. LLOYD, M.A., 5T8

Introduction

The clinical features of dermatomyositis as a rule, are sufficiently characteristic to permit a correct diagnosis to be made, although it can only be verified by pathological examination. The primary process consists of a diffuse degeneration of the skeletal muscles accompanied by a variable degree of nonsuppurative inflammatory reaction. This leads to the clinical picture of severe muscle weakness and frequently muscle tenderness. There may be associated cutaneous lesions. The onset may be acute with rapidly progressive peripheral and visceral symptoms or it may be insidious with low grade symptoms and slow progression. Some patients run an intermittent course with partial remissions. Complete remission is rare in adults although it is observed more frequently in children.

Removal of a coexisting malignant tumor has been followed by the disappearance of symptoms in a few patients in whom the disease has been associated with a malignant process. Residual muscle inflammation, fibrositis, and secondary joint changes in the chronic stage may lead to permanent disability.

The outcome is fatal in most cases within a period of three to five years.

Etiology

The etiology is not known. Bacterial, parasitic, and viral infections have been implicated in an attempt to explain the pathogenesis of the disease. Organisms singled out have included streptococci and staphylococci. No single organism, however, with a latent period between infection and onset of generalized symptoms is reeognized in the pathogenesis of dermatomyositis, such as is the case in acutc rheumatic fever for example.

A hypersensitivity to toxins, drugs (especially the sulphonomides and penicillin) and sunlight have been proposed but the evidencc is scanty.

Pathology

The skeletal muscles grossly appear pale and edematous with the musele bundles separated by edema fluid. There is degeneration of muscle fibrils with fragmentation, loss of striations, separations of the myofibrils with edema, infiltration with lymphocytes, and large mononuclear cells. Coagulation or hyalinization of the sarcoplasm appears in some instances and there may be perivascular infiltration by lymphocytes, plasma cells, and histiocytes around arterioles. The vessels may show thickening of the intima with narrowing of the lumen, and occasionally thrombus formation.

It should be noted that significant microseopie ehanges may not be present in muscle biopsy obtained during the early stages of the disease but pathologic changes with widespread destruction are apparent if muselc tissue is examined after the process has been present for several months or longer.

Vital muscles of deglutition and respiration may be involved: viz. pharyngeal muscles and diaphragm, and this may promote terminal pneumonia. Heart muscle may likewise be involved. The skin changes may resemble those of scleroderma. There is thinning of each of the layers with atrophy and keratosis, follicular plugging, and degenerative or inflammatory changes in the collagen tissue.

Lesions in the intestinal tract have been demonstrated: viz. ulcers of the esophagus, stomach, small bowel and rectum. These ulcers have been associated with edema and cellular infiltration of the walls of arteries and veins which lead to mucoid and fibrous thickening of the intima, with narrowing of the lumen and thrombosis. A focal or diffuse myocarditis may be present. Examination of the liver may show perilobular infiltration, and of the spleen may show congestion and infarction. The kidneys are rarely involved but may show an endarteritis of the interlobular arteries.

Clinical Findings and Course

The disease often begins insidiously with low grade fever, malaise, aches and pains in the extremities, without any significant preceding medieal event; or the onset may be abrupt, with edema and an erythematous rash on the face as the presenting complaint. Most patients complain of muscle aehing, muscle weakness and fatigue. Cutaneous manifestations are present at some stage of the disease in most instances and are independent of the muscle involvement. Erythema may be present with or without subcutaneous edema and may be mottled or diffuse, livid or rosy. The face and the 'V area' of the neck are the commonest sites to be involved, but the extensor surfaces of the arms and legs and even the trunk may be affeeted. During the natural course of the disease these cutaneous manifestations undergo alteration and at a later stage there may be pigmentation and telangiectasia.

Muscular weakness is usually a prominent feature but may be mild and

insignificant in some cases. Any striated muscle may be involved with a tendency for the weakness to be bilaterally symmetrical. The large muscle masses are more frequently involved than the pharyngeal, laryngeal, intercostal, diaphragmatic or ocular groups. In the limbs, the proximal muscle groups of the upper and lower extremities are more likely to be involved than the distal groups.

Most patients have a diffuse muscle tenderness. There often appears to be a dissociation between subjective and objective evidence of muscle involvement: viz. extensive involvement upon microscopic examination has been discovered in muscles that have been neither painful nor tender. Because of the weakness of skeletal muscles the patient may walk with an unsteady, shuffling gait and may even fall while walking. With severe weakness the patient may not be able to sit up in bed or hold up his head. Weakness of the facial and glossal muscles makes eating and speaking difficult, and extensive involvement of the muscles of respiration and deglutition may predispose to dysphagia and regurgitation of food.

If the disease follows a subacute or chronic course, severe atrophy of the muscles and extensive fibrosis with contractures at the elbows, knees, hips, and fingers may develop. Involvement of the upper respiratory tract may give rise to symptoms of dyspnoea, hoarseness or an alteration in the pitch of the voice. The smooth muscle of the gastrointestinal tract may also be affected, producing symptoms indistinguishable from systemic scleroderma: viz. stomatitis, myositis of the tongue, dysphagia and epigastric distress.

Enlargement of the liver, spleen and lymph nodes may be noted in some patients. Neurological manifestations may include confusion, delirium or psychosis. It might be noted that the muscle weakness of myasthenia gravis or severe thyrotoxicosis sometimes bears a similarity to that of dermatomyositis.

The average life expectancy under current methods of therapy in a patient without malignant tumor is about three to five years from the onset of clinical symptoms. Survival may be prolonged for ten years or more when the disease becomes subacute or chronic. Complete remissions, with apparent restoration of health, are rare but have been observed to occur spontaneously, with steroid therapy, or following removal of a malignant tumor. In the acute fulminating cases with severe weakness, death frequently results from intercurrent infection, cardiac failure, or respiratory insufficiency. Weakness or paralysis of the pharyngeal and intercostal muscles may result in regurgitation and aspiration of products of digestion with the development of an aspiration pneumonia. In the chronic phase malnutrition and invalidism from contractures contribute to the morbidity.

Diagnosis

The disease should be suspected in any patient with atypical musculoskeletal complaints especially when associated with muscle weakness or tenderness. The presence of muscle weakness and tenderness, particularly of the shoulder girdle and pelvic girdle, together with skin lesions, fever and malaise, should suggest the diagnosis. Enquiry should be made in regard to a history of Raynaud's symptoms or antecedent facial or periorbital edema. In all suspected cases, biopsies of muscle and skin should be obtained, since this is the only means of establishing the diagnosis beyond doubt. However, a negative biopsy in a patient with typical symptoms of dermatomyositis does not always exclude the diagnosis.

The disease must be differentiated from systemic lupus erythematosus, rheumatic fever, systemic scleroderma, trichinosis, thyrotoxic myopathy, progressive muscular dystrophy, amyotrophic lateral sclerosis, myasthenia gravis, and Addison's disease.

Relation to Neoplastic Disease

The frequency with which dermatomyositis has been observed in association with malignant tumors is considerably higher than can be accounted for by the element of chance. This is in marked contrast to the other collagen diseases. It has been postulated that "tumor toxins" are responsible for the musculocutaneous disorder and in some instances symptoms have been observed to improve temporarily following removal of tumors (one carcinoma of the ovary, one carcinoma of the breast). It is estimated that a malignant process may coexist in about 18 percent of patients with dermatomyositis; carcinoma of the ovary and breast being the most frequent tumors. Presumably this is a function of the sex incidence of dermatomyositis and indicates the frequency of malignancy of the primary and secondary sex organs in females. In males carcinoma of lung, esophagus, stomach, colon, rectum, and kidney have been noted. Other tumors associated with dermatomyositis include Hodgkins' disease, multiple myeloma, retroperitoneal sarcoma, carcinoma of parotid gland, carcinoma of liver, sarcoma of bone, carcinoma of cervix, and a chromophobe adenoma of the hypophysis.

Treatment

The treatment of patients with dermatomyositis has on the whole been discouraging. Analgesics such as salicylates may give some relief when pain is a prominent feature, and in some instances opiates may be indicated. General supportive measures include adequate rest, avoidance of excessive fatigue, physiotherapy, supportive splints and corrective operative procedures when contractures are present. The diet should be adequate and infections should be dealt with promptly.

No specific agents have been shown to have a consistent beneficial effect in this disease. ACTH, cortisone, hydrocortisone and related steroidhormones have been shown to exert some ameliorating effect on the course of the disease in most patients. Fever may subside, pain may be relieved and muscle power improved. In the majority of cases, the improvement is only partial and may not be lasting, although in a few instances it may be dramatic. However, in view of the lack of other specific measures, a trial with these hormonal agents is justified in all cases. The use of testosterone as an anabolic agent, in conjunction with corticosteroid therapy has been advocated.

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SUPPLEMENTARY SECTION

PSYCHOTHERAPY—KINDS OF THERAPY

D. CAPPON, M.B.

(Second article of the series)

*"Quod homines tot sententiae".**

(As many heads, so many opinions)

IT was not very long ago when the watchwords were "Mens sana in corpore sano" (a healthy mind in a healthy body), and physicians prescribed for their "nervous" patients fresh air, diet, and a change of air to a balnearic resort, cum the proverbial pat on the back and the devastatingly cheerful exhortations: "Chin up! You will grow out of it! It's nothing at all; just in the mind, forget it. It's overwork!"

Since then wisdom has come in dribs and drabs. Some physicians have realized that the above advice could be fatal to the patient who escapes into tantalic efforts or profitable endeavour from the ugly phantasms of his unconscious, the shapes of his diabolic conscience and an inner conviction of the weakness and unworthiness of his own self. Just when such a patient is decompensating, that is when his intrapsychic malignant forces are about to burst through the bastion of ego defence erected by Work, and thus just when he is rendered defenceless, prey to inner conflict, a sudden interruption by a vacation may precipitate an acute depression, all the way down from a penthouse floor to the ground.

Other perspicacious physicians have observed how an acute emotional upset may be precipitated by the release of life-long tensions just when, after years of struggle, all goes well and there is a respite.

A general measure of agreement exists, despite pontifical opinions, or anti-psychiatric bias, that it might be a good thing to attempt to understand the nature of a psychologic upset or disorder and correct it, psychologically, if possible. To achieve this, rapport with the patient is necessary. A number of techniques may be applied to achieve rapport and subsequent understanding. Whether one concedes or not the paramount role of the unconscious (levels of unawareness) in the genesis of mental upsets, it is generally regarded as therapeutic and preventive of further mischief to lead the patient to an application of the exhortation inscribed above the entrance to the Temple of Apollo at Delphi: "Gnothe seautum aur meum agan" (Know thyself and nothing to excess).

Now experts and others differ, often for personal reasons and reasons of their own dynamic conflicts leading to bias, as to the ways and means of psychotherapy. Yet what follows is a generally agreed upon broad classification of techniques—a pitiably small tool-kit for the psychotherapist.

*The relatively numerous quotations are given apart from their questionable value in liberal education in order to appreciate that nothing is entirely new, least of all Psychotherapy. Its newness is a more or less orderly and explicit organization.

Classification of Type of Pschologic Treatments and Aids

A. Physical adjuvants

1. *Medication*

(a) specific—like Dilantin for epilepsy or antabuse for alcoholism.

(b) symptomatic—like tranquillizers for tension-states and hynotics for insomnia.

2. *Inhalation therapy*

(a) Narcoanalytic—like N_2O or ether for psychic exploration.

(b) Abreactive & Deconditioning—like 70% CO_2 and 30% O_2 for some neuroses.

3. *Intravenously induced narcosis*—for psychic exploration and abreaction.

4. *Stress Techniques*—like chrymotherapy (body freezing) or stroboscopic flicker exposurc, adrenalin etc. for deconditioning and to induce resistance to stress.

5. *Electroplexy*—and other convulsive procedures to induce epileptic fits and coma for depressions, especially involutional melancholia.

6. *Insulin*—

(a) "modified" for sedation, weight increase and "subcoma" or sopor useful in certain neuroses.

(b) "coma"—to induce regression and "shock" in schizophrenia.

7. *Neurosurgery*—like unilateral and bilateral lobotomy, and other procedures for acutely disturbed psychotics.

As the word "adjuvant" implies, these measurcs—save the neccssary medication for the treatment of concomitant organic disorder—are arrayed in order of incrcasing violence, increasing and often therapeutic punitiveness, all thc way to mutilation. These methods are used in lower and lower octaves of despair in the hope of subsequently "helping" the patient towards somc sort of psychotherapeutic rapprochement.

Alas, in the anxious prelude of exhibiting an empirical artifice to bring back the patient to minimal normality for adequate social and verbal communication, the main purpose, namely the making of psychotherapeutic contact, is too often forgotten. Consequently early remissions are followed by early relapses which in turn might not have occurred if the remissions had been allowed to take place naturally, as happened in the old days of custodial care and nihilism. In the anxiety to prevent suicide and to relieve the strains on the staff of hospitals, it is not possible to estimate how much damage may be incurred by the patient submitting repeatedly to the more "shocking" physical methods. Certainly where the aim is amnesia, a tabula rasa for healthier living, or a more vegetable-like emotional state, damage, at least to the intellect, is inevitable. This is not to say the psychiatrist can do without these primitive empirical physical methods, faute de mieux. But it is to say that even the most seemingly innocuous physical measures, such as tranquillizers, when they interfere effectively with a complex psychological process, such as a neurosis, when they interrupt, say, the pathways of anxiety, masking and defending against an underlying depression, can be dangerous.

And it is to say that it does not seem likely that a whole twisted and pathological life experience resulting in a neurosis or one of the truly "functional" psychoses, can ever be wiped away, and the mind organically or mechanically rearranged to "adjust" as it has never adjusted before (for breakdowns in living have roots rotted at the beginnings of life) by the mere exhibition of physical methods of interference. And it is to say that I believe that whereas these measures are relatively expedient

now, they are destined to pass into the annals of psychiatric history as hallmarks of a Dark Age. Finally, at present I do not see how lives which have been psychologically distorted can ever be corrected except by the most painstaking of psychologic means. The only alternative is not to allow psychopathologic distortions to occur in the first place, by the judicious application of preventive psychosocial measures.

B. Psychotherapy proper

Divisions depend on number of variables, thus:

1. The nature of the disorder and the severity of illness determine, among other things, whether:

(a) The setting be a hospital, or a clinic or the consulting room.

(b) The goal be integrative, i.e., radical, aimed at personality change; or palliative, aimed at a reduction in symptoms.

(c) The technique be exploratory, uncovering, non-directive, or supportive and/or directive.

(d) The time be brief, i.e., 3 months or less, or long term methods.

(e) The therapist be especially trained, i.e., dynamic and skilled in analysis and especially endowed, or not.

2. The age of the patient determines such settings as the play-room for a child; such techniques as counselling adolescence, or for senescence problems.

3. The personality setting of the specific complaint, determines in part such choices as group vs. individual therapy and it determines the goals set. The patient's personality may exclude (through likely clashes or mutual allergies) certain therapists on the grounds of their personality. A low level of intelligence in the patient limits the scope of more ambitious psychotherapy, but not necessarily its general effectiveness. On the other hand, a high level intelligence in the patient most certainly limits the field of available therapists, even if Doctors are wrapped in white coats with a stethoscope nonchalantly dangling from a pocket, for to possess these magic emblems they needed no more "g" (General intelligence) than some 110 basic points of I.Q. to complete a medical education.

4. The sex of the patient and the related complaint, may determine the preferable sex of the therapist initially and later on in treatment.

5. The psychosocial setting of the patient, may determine the approach; for instance a new immigrant's problems could be lessened or relieved often by environmental manipulation without much intrapsychic interference. Too big a class distinction between patient and Doctor is a considerable barrier. Ethnic and language distinctions are another barrier, and religious differences make for considerable difficulties.

6. The financial status of the patient, determines largely the setting whether private or public. If and when the State pays all, then, of course, there will be no limit to patients nor to the length of comfy therapy.

7. The patient-load, of a clinic or private therapist determines willy-nilly the time taken, i.e., brief or long methods; the number treated simultaneously, i.e., groups or individuals, and the technique used: varying from fashionable sniffs at the latest physical method to prolonged couch-talking.

8. The therapies available in any clinic or office limit the choice.

9. The therapist, his skill, his patience, his training, his bias, his age and stage in development of wisdom, his dedication to common or horse-sense vs. uncommon intuition; or to suave tact vs. honest truth; or conventionalism and

bias vs. freedoms, will largely dictate the choice and possibility of therapy.

Perhaps the most fortuitous factor for the unsuspecting patient, blind to the subleties both in himself and in his future therapist, which antedate his fateful encounter in therapy which is to alter his paths in life, is the pattern of connection made between therapist and referring physician.

One need not wonder at the hinterland vagarity of this process when one remembers that in psychotherapy it is the Doctor who is the patient's pill.

To regroup the techniques of psychotherapy:

A. *Number of patients*

Individual or group methods (analytic, social groups, psychodrama, etc.).

B. *Time*

Short term (abreactive, hypnotic, analytic, etc.) or long term, more than 3 months.

C. *Goal*

Integrative, or palliative, or more often both.

D. *Methods*

Directive (Counselling, prescribing living designs, inspirational, etc.).

Non-directive (analytic, uncovering or counselling).

Anaclitic (encouraging and acting out regression, and subsequently resynthesis).

"Deconditioning", or better "Dehabituating": (as in treatment of stutterers, or play backs of insightful statements, or reliving war experiences in sound or on screen, or brain washing, etc.).

Play therapy (using toys for communication).

Psychosomatic techniques (simultaneous application of brief methods of psychotherapy and physical treatment and/or anaclitic therapy).

"Guidance" (as for children, adolescence and in old age) or for vocation, for marriage, before marriage and for industrial problems, etc.

Social Therapy (use of social workers, "manipulation of the environment", use of large groups for "aculturation and socialization", etc.).

Occupational Therapy.

The use of fine Arts: musico-therapy, use of painting both as occupational and as abreactive and investigatory techniques, etc.

Bibliotherapy and self-analysis—usually a supportive method reinforcing the neurosis. Gymnastics, Hydrotherapy, Physiotherapy.

The list, quite obviously cannot be comprehensive. Not only are there many variants on each theme, but also it would extend into all those methods man has for occupying and diverting his mind, for enjoyment and for creative activity.

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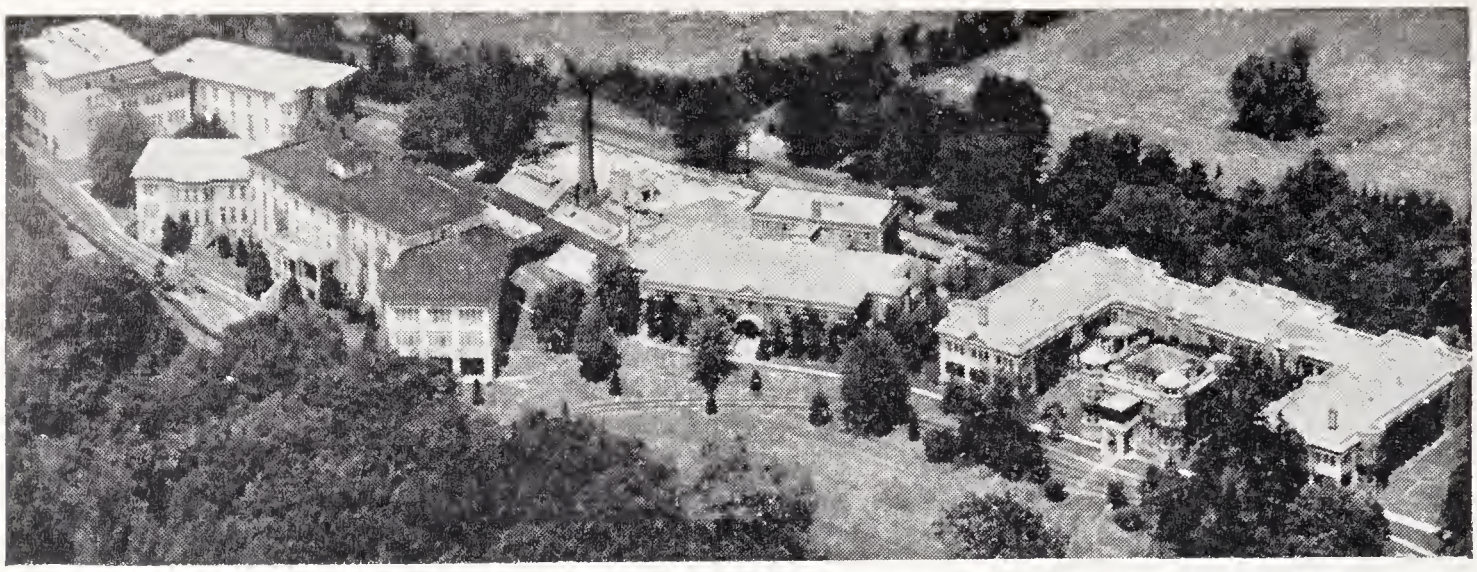

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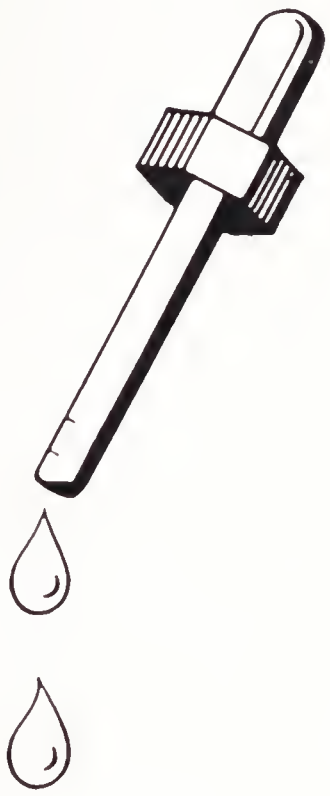

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